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Progress Report
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The following report is a continuation of the progress report submitted June 1, 1958, which described briefly the hypothesis to be tested, the method of investigation, the drugs studied, and the number of experiments.

I

This phase of the project was to test the effect of d-LSD-25 and related compounds on the subcortical electrograms to see whether there could be demonstrated correlations between paroxysmal hypersynchronous activity in the septal and/or hippocampal region and known psychotomimetic effect.

A. d-LSD-25 (d-lysergic acid diethylamide)

This drug was given in doses of 70 to 110 gamma per kilo on five different occasions. In two instances there was dramatic catatonic behavior, and in both these instances there was 7 to 20/second paroxysmal hypersynchronous activity in the hippocampus and septal regions. This was also reflected in the frontal cortical region. In another instance, the catatonic behavior was slight but definite, and again there was 7/second hypersynchronous activity in the hippocampus and septal region, but this time it was reflected in the parietal region. On two other occasions, the animal was either drowsy or agitated. In these instances, there was paroxysmal activity in the frontal and the hippocampal regions, but it was absent in the septum. From these studies on d-LSD, it would seem that the crucial location of electrographic activity is the septal region -- the more marked the changes in this region, the more marked the behavioral changes in the animal, particularly catatonic behavior.

B. ALD-52 (d-1-acetyl-lysergic acid diethylamide)

This drug was given in doses from 140 to 500 gamma per kilo. On the basis of research done at the National Institute of Mental Health by Harris Isbell as reported by the Sandoz Company, this drug shows 13% of the pyretogenic activity, 200% of the antiserotonin activity, and 100% of the psychotomimetic activity of d-ISD-25. Three studies were done. In all three instances the animal became agitated. With this agitation was 12/second paroxysmal activity in the frontal, parietal and hippocampal leads, with only minimal reflection in the septal leads. No catatonic behavior was observed.

C. MLD-41 (d-1-methyl lysergic acid diethylamide)

This drug was given in doses ranging from 50 to 200 gamma per kilo. The drug shows 5% of the pyretogenic, 370% antiserotonin effect, and 40% psychotomimetic effect of d-LSD-25. Two studies were done. In both instances the animal became quite placid again showing 12/second paroxysmal activity in frontal and hippocampal regions with slight involvement of the septal region. This placid behavior was interpreted as minimal catatonic behavior.

D. LSM (d-lysergic acid morpholide)

This drug was given in doses of 180 to 450 gamma per kilo. It shows 10% of the pyretogenic, 2% of the antiserotonin, and 20% of the psychotomimetic effect of d-LSD-25. In two studies, the animals both showed rather dramatic, flaccid or early catatonic response. In both instances, there was dramatic slow activity throughout the record, and slight paroxysmal activity in the hippocampal region and septal regions.

E. DAM (d-lysergic acid dimethylamide)

This drug was given in doses ranging from 40 to 200 gamma per kilo. The drug shows 43% of the pyretogenic, 23% of the antiserotonin, and 10% of the psychotomimetic effect of d-LSD-25. Three studies were done on this drug, two

of which showed dramatic behavioral change, one animal becoming extremely restless, another showing definite catatonic effect. In these two animals there was dramatic paroxysmal activity reflected in the septal region at the frequency of 12/second. This activity was also apparent in the frontal, parietal and hippocampal regions. In a third animal that showed somewhat less behavioral change, mostly restlessness, there was paroxysmal activity in the frontal and hippocampal regions, but none in the parietal or septal regions. These studies are important because allegedly the drug has little psychotomimetic effect. However, on the animals, they showed dramatic behavioral changes and also striking changes in the septum.

F. LPD (d-lysergic acid pyrrolidide

This drug was given at a dose level of 40 gamma per kilo. It has 10% of the pyretogenic effect, 5% antiserotonin effect, and 10% psychotomimetic effect of d-LSD-25. One study was done. This animal showed dramatic flaccid response and had slow paroxysmal activity of 6/second appearing in the frontal, parietal, septal and hippocampal regions with also generalized slow background activity. Again this is another example of dramatic EEG changes and behavioral changes in a drug that is reported on humans to have little psychotomimetic effect.

G. 1-LSD-25 (l-lysergic acid diethylamide)

This drug was given in dose ranges of 300 to 450 gamma per kilo. It is allegedly inactive and this seemed to be confirmed by the EEG findings, there being no changes and no behavioral effects.

H. BOL (d-2-bromo lysergic acid diethylamide)

This drug was given in dose ranges of 110 to 175 gamma per kilo. The drug supposedly has 5% of the pyretogenic effect, 103% antiserotonin effect, and 0% psychotomimetic effect of d-LSD-25. In the three studies done, there

was no obvious behavioral change. However, on one of the three studies, there were slight EEG changes with spindles of 15 to 25/second appearing in the parietal cortex.

Discussion

From the above studies, it would seem that there was a good correlation between septal paroxysmal activity and dramatic disturbances in the behavior of the monkey, particularly catatonic like behavior. However, several times when catatonic behavior was not obvious and marked agitation was present, there also occurred at least some changes in the septal region (ALD-25, MLD-41, and DAM). The animal might show fairly dramatic changes, particularly in terms of becoming flaccid if there was generalized slowing in all leads. However, if the drugs had no effect like 1-LSD-25 and BOL, there were no behavioral changes nor were there any EEG changes. Thus, it seems obvious that there is some correlation between behavioral changes and paroxysmal activity in the hippocampal and septal region. However, this is not correlated with the alleged psychotomimetic effect in humans. That is, DAM and LPD gave dramatic responses in the monkeys although they are supposed to have relatively little psychotomimetic effect on human beings. It would seem to me that this data reported by Isbell should be checked again on human beings in view of these animal studies. The EEG changes do not seem to be related to the antiserotonin effect, as for instance BOL gave no response and MLD as well as ALD, both of which have high antiserotonin activity, gave little in the way of septal changes, as compared with DAM and LPD which have relatively little antiserotonin effect. However, reports from Sandoz do suggest that DAM and LPD have marked autonomic effects. This suggests a possible correlation between septal paroxysmal activity and increased autonomic activity. There is one other possibility and that is that the DAM and the LPD effect might

be due to the hypotensive effect of these drugs.

An unrelated compound chemically, but one with dramatic psychotomimetic activity, namely mescaline, was also given in three studies with a dose range of 9 to 22 milligrams per kilo. One of the studies was equivocal. However, a second showed definite catatonic behavior with 6 to 8/second paroxysmal activity in the frontal, septal, and hippocampal regions. The third animal became quite lethargic and then developed convulsions. Spiking activity occurred in the frontal, septal and hippocampal regions, ultimately to be replaced by generalized seizural activity.

II

The second phase of this study was to test the effect of serotonin on the animal by giving a monoamineoxidase inhibitor (phenylisopropylhydrosine) combined with a serotonin precursor 5-hydroxytryptophane which crosses the blood brain barrier. Three studies with the PIH at 5 milligrams per kilo were done. In two there was no change, while in the third there was some agitation with 15 to 25/second spindle activity in the fronto-parietal region. 5-hydroxytryptophane was given in dose ranges from 10 to 20 milligrams per kilo. In one instance there was generalized slowing; in the other instance no change, nor were there any marked behavioral changes. However, in two studies where the 5-hydroxytryptophane and the PIH were combined in the dose levels mentioned above, the animals were slightly retarded and did show, besides slow delta activity in all leads, a slight tendency to spiking followed by a slow wave in the septal and hippocampal region. This response, because of its equivocal nature, will have to be tested on several other monkeys.

However, there is one other interesting finding which should be mentioned

here. That is, when an animal was given BOL eleven days after the above combination, there was a decided difference in the response to the BOL. That is, within 20 seconds, there were bursts of high amplitude, sharp 16 to 17/second activity in the frontal and hippocampal region, looking similar to barbiturate spindles. The amplitude was greater than 200 microvolts at the height of the reaction, and was almost continuous at that time. Repeat studies to verify this finding are now in progress.

III

Three studies were done giving animals EA-1476 in doses ranging from 125 to 500 gamma per kilo. In the first instance there was extreme agitation, but only generalized high amplitude 1½/second waves with waxing and waning. However, in the two other experiments, there was marked flaccidity with suggestive catatonic reaction with spike and slow wave formation in the septal and hippocampal region as well as this high amplitude 1½/second waxing and waning generalized response. This would suggest that EA-1476 which affects the septal and hippocampal region much as d-LSD-25 does might have dramatic psychotomimetic effects. As there was some inconsistency in the response of animals to this drug, further tests of this kind are now in progress.

In conduct of [illegible] this report, the [illegible] tory [illegible] the Committee on [illegible], Research, National Academy of Sciences-National Research Council.